The natural history of milk allergy in an observational cohort

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Abstract

Objective—There are few studies on the natural history of milk allergy. Most are single-site and not longitudinal, and these have not identified a means for early prediction of outcomes.

Methods—Children aged 3 to 15 months were enrolled in an observational study with either (1) a convincing history of egg allergy, milk allergy, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis (AD) and a positive SPT response to milk or egg. Children enrolled with a clinical history of milk allergy were followed longitudinally, and resolution was established by means of successful ingestion.

Results—The cohort consists of 293 children, of whom 244 were given a diagnosis of milk allergy at baseline. Milk allergy has resolved in 154 (52.6%) subjects at a median age of 63 months and a median age at last follow-up of 66 months. Baseline characteristics that were most predictive of resolution included milk-specific IgE level, milk SPT wheal size, and AD severity (all $P < .001$). Baseline milk-specific IgG_4 level and milk IgE/IgG_4 ratio were not predictive of resolution and neither was expression of cytokine-inducible SH2-containing protein, forkhead box protein 3, GATA3, IL-10, IL-4, IFN-γ, or T-bet by using real-time PCR in CD25-selected, casein-stimulated mononuclear cells. A calculator to estimate resolution probabilities using baseline milk IgE level, SPT response, and AD severity was devised for use in the clinical setting. Conclusions: In this cohort of infants with milk allergy, approximately one half had resolved over 66 months of follow-up. Baseline milk-specific IgE level, SPT wheal size, and AD severity were all important predictors of the likelihood of resolution.

Keywords

Milk allergy; natural history; food allergy; IgE

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Milk allergy is the most common food allergy in young children, with prevalence rates estimated in the range of 2% and 3%.[1,2] Although the natural history of milk allergy is generally favorable, with the majority of children showing resolution during childhood, prior studies have yielded widely varying results as to the rate of resolution.[3-16] A recent study suggested that the natural history of milk allergy might have changed over time, with slower rates of resolution and a higher proportion of children with disease persisting into adolescence and even adulthood.[15] Although these changes might be real, most differences between studies are more likely related to both study design and the specific population under investigation. For example, studies of the general population,[11] especially if oral food challenges are performed at regular intervals, are more likely to demonstrate earlier resolution than studies of tertiary referral populations.[3,9,10,15]

The Consortium of Food Allergy Research enrolled infants with likely egg or milk allergy but without previously known peanut allergy in an observational study to address the immunologic, genetic, and environmental factors that affect the natural course of food allergy.[17] The primary aim of this analysis was to assess the natural history of milk allergy in the infants enrolled in this cohort with a diagnosis of milk allergy, with a particular focus on the clinical factors predicting the resolution of milk allergy over the first 5 years of life.

METHODS

Subjects, study definitions, and procedures

The subjects of this study are a subset of a larger cohort of 512 infants originally enrolled at 3 to 15 months of age at 5 sites: Mount Sinai School of Medicine, New York, New York; Duke University Medical Center, Durham, NC; Johns Hopkins University School of Medicine, Baltimore, Maryland; National Jewish Health, Denver, Colorado; and Arkansas Children's Hospital, Little Rock, Arkansas, as described previously[17]; the North Carolina subjects moved with the investigative team from Duke to the University of North Carolina–Chapel Hill in March 2012. Enrollment criteria for the whole cohort were designed to obtain atopic children with likely egg or milk allergy at risk for peanut allergy but without current peanut allergy. Briefly, enrollment required either (1) a history of a convincing immediate allergic reaction to cow's milk (and/or egg) and a positive skin prick test (SPT) response (3 mm larger than that elicited by the negative control) to cow's milk (and/or egg, if the clinical reaction was to egg) and/or (2) moderate-to-severe atopic dermatitis (AD) and a positive SPT response to milk, egg, or both.

The subgroup of children in the current study had a diagnosis of milk allergy at the time of enrollment or acquired this diagnosis after enrollment with no prior evidence of tolerance of milk (eg, enrollment diagnosis was uncertain). Study procedures were reviewed and approved by a National Institute of Allergy and Infectious Diseases Data Safety Monitoring Board and by local institutional review boards, and written signed consent forms were obtained.

Participants were considered to have milk allergy if they had either (1) a positive physician-supervised oral food challenge result or a convincing reaction (defined by symptoms within an hour of isolated ingestion that included at least urticaria and/or angioedema, difficulty breathing, wheezing, throat tightness, and/or vomiting) and sensitization to milk (milk-specific IgE level ≥ 0.35 kU_A/L and/or SPT response >3 mm) or (2) a flare of AD associated with milk ingestion along with a milk-specific IgE level of greater than 5 kU_A/L,[18] which is greater than 95% predictive of milk allergy in infants. Reactions to goat's or sheep's milk were also considered evidence of cow's milk allergy. Subjects were considered milk tolerant if they ingested whole uncooked milk products (milk, yogurt, or ice cream) in serving size

quantities without symptoms either during physician-supervised oral food challenges or after introduction at home. Dietary ingestion of products with extensively heated milk (baked milk, for example as an ingredient in a muffin) was queried but was not considered evidence of resolved milk allergy.

Dietary, medical, and social histories were obtained by using questionnaires completed during enrollment interviews. A diagnosis of asthma and allergic rhinitis was based on parental report or parental report of a physician's diagnosis. A diagnosis of other food allergies included per-protocol definitions for egg and peanut,[17] whereas for other foods, this was based on a clinical diagnosis by a study physician.

Diagnosis of AD required pruritus and an eczematous rash (acute, subacute, or chronic) with typical morphology and age-specific patterns, a chronic or relapsing history, atopy (personal history, family history, or both or IgE reactivity), and xerosis. AD severity was graded based on criteria previously described and published by Rajka and Langeland.[19] Briefly, the AD severity was graded as mild, moderate, or severe by using the following parameters (see Table E1 in this article's Online Repository at www.jacionline.org) [19] to compute a score summation: (1) extent of disease (by "rule of nine" based on the proportion of body surface area with active disease), (2) course of disease (defined by history as >3 months in remission in the past year, 3 months in remission but not continuous, or continuous remission over the past year), and (3) intensity of disease (defined as mild itch rarely disturbing sleep, severe itch usually disturbing sleep, or intermediate itch/sleep disturbance), each on a 3-point scale. Summation scores of 3 to 4 indicated mild disease, 5 to 7 indicated moderate disease, and 8 to 9 indicated severe disease. Atopic disease history in parents of the enrolled infants was based on previously published definitions and was recorded by parental report.[20]

The study design includes evaluations, care for food allergy, and instructions on dietary management that were uniform among the 5 clinical centers and reflect practice parameters for AD,[21] food allergy,[22] and the American Academy of Pediatrics recommendations for allergy prevention published in 2000 to maintain uniformity and an observational approach.[23] Participants were evaluated in person at enrollment, 6 months, 12 months, and yearly thereafter, with additional telephone follow-up between each visit and instructions to contact the study site for any allergic reactions, at which time additional details were obtained.[24]

SPTs

SPTs were performed with the GreerPick (Greer Laboratories, Lenoir, NC), with participants avoiding antihistamines for at least 5 half-lives of the specific agent. Tests were performed on the infant's back, and at 15 minutes, the wheal was outlined in pen and transferred by tape to paper. The size of the longest diameter and its longest perpendicular were averaged. An SPT score was computed by subtracting the saline control measure, and a positive SPT response was defined by a score of 3 mm or greater. Tests were considered reliable if the wheal of the negative control (50% glycerin-saline) was 3 mm or smaller and wheal size elicited by the histamine control was at least 3 mm larger than the wheal size elicited by the negative control. All sites used the same lot of reagents, and training was performed to ensure consistency. The cow's milk extract was obtained from Greer (catalog no. F293).

Serum milk-specific IgE and IgG$_4$ levels

The concentration of specific IgE antibody to milk was measured from plasma at a central laboratory (Mount Sinai) by using the Phadia (now Thermo Fisher Scientific, Waltham, Mass) ImmunoCAP system and reported in kilounits of allergen per liter. A level of 0.35

kU_A/L or greater was considered positive. The concentration of IgG_4 antibodies to milk was also measured from plasma samples by using the Phadia ImmunoCAP system. The detection limit for IgG_4 is 0.07 mg/L.

Mononuclear cell stimulation and PCR analysis

PBMC isolation was performed with Ficoll-Paque density gradient centrifugation, and cultures were performed at each clinical site on fresh venous blood samples, as previously described.[1] Briefly, 4 million cells per condition were cultured for 48 hours in AIM-V serum-free media (Invitrogen, Carlsbad, Calif) with purified α-, β-, and κ-caseins (50 μg each/L), and control stimulations were performed with medium alone (negative) and anti-CD3/anti-CD28 beads (positive). At the end of the culture period, cells expressing CD25 were enriched by means of selection with anti-CD25–coated paramagnetic beads, according to the manufacturer's protocol (Miltenyi Biotech, Bergisch Gladbach, Germany). Pilot experiments demonstrated approximately 10-fold enrichment of $CD25^+$ cells, with 70% to 80% of selected cells coexpressing CD3, CD4, and CD25, as measured by using flow cytometry. The entire selected fraction of cells was immediately lysed in RLT buffer (Qiagen, Hilden, Germany) and stored at −80°C until RNA purification. The quantitative PCR was carried out in the central laboratory according to the in-house established protocol by using SYBR Green I fluorescence detection in a 384-well plate on the ABI 7900 (Applied Biosystems, Foster City, Calif). Raw PCR analysis and annotation were performed on coded samples. The cycle threshold (Ct) number was set by software, with confirmation and adjustment as necessary to define the threshold of linear amplification. For the gene expression data, $\Delta\Delta$Ct was calculated by subtracting the RPS9 reporter gene Ct value and then normalizing by subtracting the standardized medium control response. Negative values indicate relatively higher activity with a unit score change corresponding to a doubling. Nondetected genes were arbitrarily assigned a Ct value of 40.

Statistical analysis

Time to resolution of milk allergy was measured with age as the time metric. Although the time of allergy diagnosis varied depending on when food introduction and diagnostic testing were performed, each subject's first definitive diagnosis was positive for milk allergy. Those subjects (n = 12) who had resolution of their milk allergy before 15 months were assigned a value of 15 months. Because enrollment continued through 15 months, this permitted the use of fixed covariate baseline modeling in all participants.

Distributional differences in baseline variables were compared with the χ^2 statistic. Proportional hazards regression models were fit to examine covariates for their effect on the hazard or risk function.[25] The estimated survival distribution was calculated from the relative hazard (RH), which is the exponentiated sum of the linear combination of the products of the parameter estimates with their respective clinical characteristics. The common underlying empiric cumulative hazard function $\lambda(t)$ is estimated with a step function, and the resolution curve is estimated as follows:

$$1 - \exp(-RH * \lambda[t]).$$

In this article *hazard* refers to the risk of a beneficial event, namely allergy resolution, and variables are structured so that large relative hazard values are associated with increased chance of allergy resolution. Model prediction capability for baseline variable models was summarized with the C index, a concordance measure of predicted and observed responses related to the Kendall rank correlation τ value.[26,27] This measure extends the binary end point assessment of the area under the receiver operating characteristics curve to use with

time-to-event data. The C index ranges up to 1, and a value of 0.5 indicates no predictive ability. Time-varying clinical covariate analyses used the most recent available assessment in the model, and nonproportional hazards were examined by fitting linear and spline function interactions with time. For real-time PCR variables, an additional assessment of change from baseline was performed with scores of −1 when 4 or fewer doublings occurred relative to baseline, 1 when 4 or more doublings relative to baseline occurred, and 0 otherwise. Reported P values are 2-tailed, when applicable, and SAS 9.2 (SAS, Institute, Cary, NC) and R software were used for computations.

RESULTS

Of the 512 enrolled infants, the cohort with milk allergy consisted of 293 children, of whom 244 were given a diagnosis of milk allergy at baseline. Among the remaining 49 children, the diagnosis was categorized as uncertain at their entry visit, but milk allergy was subsequently confirmed. Key baseline characteristics are summarized in Table I. A majority (178/293) of subjects were enrolled between 6 and 12 months of age; 192 were male, and 101 were female. AD was present in 261 subjects and was categorized as mild in 34, moderate in 146, and severe in 81. Twenty-four infants were given a diagnosis of milk allergy based on AD criteria, whereas the remainder had a history of an acute reaction to milk. One hundred seventeen (39.9%) subjects were also given diagnoses of other food allergies at their initial evaluation, and another 74 (25.3%) had other food allergies over the period of observation.

One hundred fifty-four (52.6%) of the 293 participants have now resolved their milk allergy, with a median age of resolution of 63 months and a median age at last follow-up of 66 months (Fig 1). All but 6 subjects had follow-up beyond 4 years of age. Resolution was defined by means of oral food challenge in 56 subjects and by successful home introduction of uncooked milk products in 98 subjects. At the 5-year time point, 32 (20.6%) of 155 subjects with unresolved allergy reported tolerating at least some baked milk products, whereas 7 reported reactions to ingestion of baked milk products.

Additional baseline characteristics of the cohort, comparing those with and without milk allergy resolution, are presented in Table I. The baseline characteristics that were most predictive of milk allergy resolution included milk-specific IgE level, milk SPT wheal size, and AD severity. Specifically, highly significant differences ($P < .001$) in the rate of resolution were noted when comparing those subjects with baseline milk-specific IgE levels of less than 2 kU_A/L, 2 to 10 kU_A/L, and 10 kU_A/L or greater (Fig 2). For example, greater than 70% of those in the lowest milk-specific IgE category had resolved milk allergy compared with only 23% of those in the highest category. Significant differences ($P < .001$) in resolution were also predicted by baseline SPT results, as shown in Fig 3, which represents a comparison of subjects with wheal sizes of less than 5 mm, 5 to 10 mm, and greater than 10 mm. In addition, marked differences in resolution ($P < .001$) were detected when comparing those infants presenting with milk allergy who had no or mild AD with those with moderate-to-severe AD (Fig 4). However, baseline milk-specific IgG_4 levels were not at all predictive of resolution (see Fig E1 in this article's Online Repository at www.jacionline.org), and the milk-specific IgE/IgG_4 ratio did not add further insight to the analyses (data not shown).

Cox regression analyses were conducted to further define the effects of these baseline variables on milk allergy resolution (Table II). Again, milk-specific IgE level, SPT wheal size, and AD severity stand out as the most important factors predicting resolution of milk allergy. For example, when analyzing milk-specific IgE level as a categorical variable, subjects with baseline levels of less than 2 kU_A/L have a 5.74-fold increased hazard ratio of

resolving their allergy versus those with levels of greater than 10 kU$_A$/L. This analysis also revealed a nonsignificant trend toward higher rates of resolution in female versus male subjects. Other variables, such as parental atopic history, education, income, and presence of siblings, were examined, and none were statistically significant predictors (data not shown).

Serial measurements of milk-specific IgE levels, SPT results, and AD severity were available to assess the significance of later results, changes over time in these variables, or both on outcomes of milk allergy (see Table E2 in this article's Online Repository at www.jacionline.org). For both milk-specific IgE level and SPT wheal size, the most recent assessments were also highly significant ($P < .001$) predictors of milk allergy resolution, whereas the associated baseline measure did not significantly contribute to the bivariate model. For these variables, the current status is therefore also important for prognosis. In contrast, the most recent AD score was not additionally predictive of milk allergy resolution when adjusted for the baseline value.

With regard to other atopic diseases, resolution was not associated with other food allergy at any time point. Resolution was slightly less likely in those who had asthma and rhinitis with hazard ratios for the time-varying most recent status covariate of 0.639 ($P = .043$) for asthma and 0.646 ($P = .022$) for rhinitis, suggesting that the development of these other atopic diseases might be associated with a decreased chance of resolution as children age. Not surprisingly, in a 2-variable time-varying covariate analysis, having baked milk without a reaction increased the chance of resolution (relative hazard, 4.1; $P < .0001$), whereas having a reaction decreased the chance of resolution (relative hazard, 0.28; $P = .072$).

T-cell studies assessed at baseline demonstrated no relationship between casein-stimulated expression of cytokine-inducible SH2-containing protein, forkhead box protein 3, GATA3, T-bet, IL-10, IL-4, and/or IFN-γ and the resolution of milk allergy (data not shown). Analyses of serial measurements of these markers also did not identify any significant predictor of milk allergy resolution.

Finally, we used the 3 baseline factors most predictive of milk allergy resolution to develop a composite score that could be applied to individual patients (see Table E3 in this article's Online Repository at www.jacionline.org). For example, as represented in Fig 5, the likelihood of milk allergy resolution for 3 individual patients is predicted by using a composite index incorporating their milk-specific IgE levels, SPT wheal sizes, and severities of AD, with lower limits for IgE set at 0.35 kU$_A$/L and SPT response at 2.5 mm. The C index for the 3-variable model is 0.724 (0.019 SE), with the single baseline variable component models ranging from 0.665 for the presence of moderate or severe AD to 0.720 for log milk-specific IgE. We have provided a Web-based calculator that can be used in counseling individual families as to the possible prognosis of their young (<15 months) child's milk allergy (see www.cofargroup.org).

DISCUSSION

In this report we have described the natural history of milk allergy in a cohort of children enrolled in an observational study with a diagnosis of milk allergy. The study demonstrates a resolution rate of just more than 50% through age 5 years, which falls somewhere in the middle of previously published studies.[3-16]

Review of those prior studies reveals 2 salient points as to why interstudy results can differ so widely. First, results of studies from general populations are more likely to show a more favorable prognosis compared with studies of children from referral populations, as are prospective studies, especially those that include regular evaluations. For example, in a Danish population-based study, 76% of infants with milk allergy had become tolerant by age

the study did not specifically encourage trial or oral food challenge to baked milk products, and therefore we believe the results reflect clinical practice.

In conclusion, we estimate from this well-characterized cohort that approximately 50% of children with milk allergy will become milk tolerant by 5 years of age. Resolution is highly associated with lower milk-specific IgE levels, smaller SPT wheal sizes, and the absence of significant AD. These highly predictive variables have been used to provide the clinician with a calculator to predict the natural history of milk allergy for individual patients under their care, although additional studies to validate the model will be needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

AD	Atopic dermatitis
Ct	Cycle threshold
SPT	Skin prick test

Clinical implications: Milk allergy is outgrown in a majority of children by school age. Baseline milk IgE levels and SPT response sizes, along with AD severity, can be used to predict the natural course of disease.
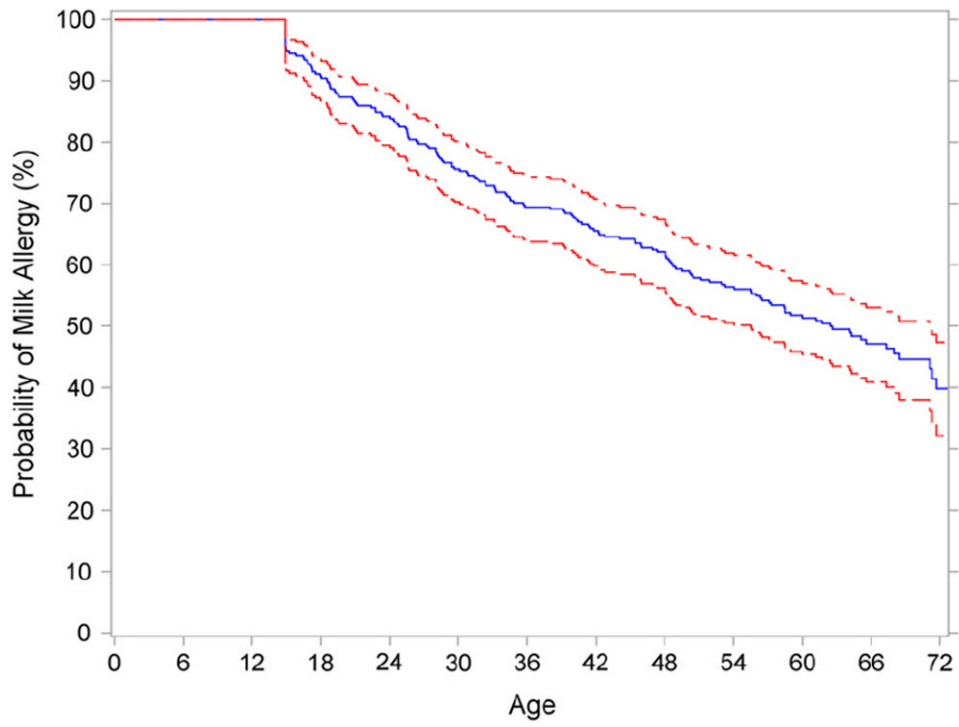
FIG 1.
Kaplan-Meier analysis of milk allergy resolution over time is shown in *blue*, with pointwise 95% CIs shown in *red*.
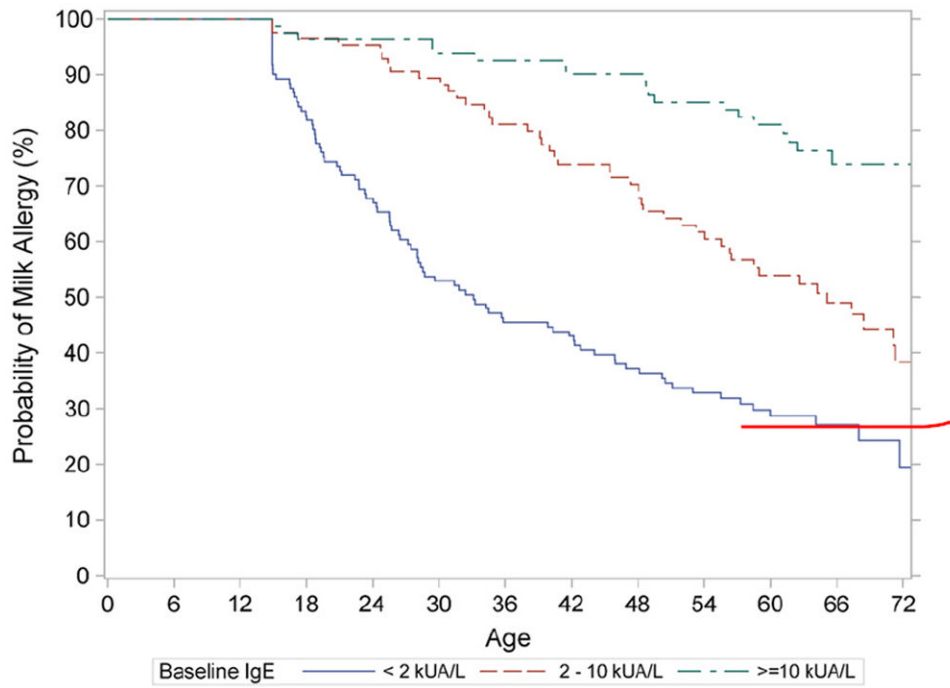
FIG 2.
Kaplan-Meier analysis representing the relationship of milk allergy resolution to baseline milk-specific IgE levels. Individual *curves* represent IgE levels of less than 2 kU$_A$/L *(blue)*, 2 to 10 kU$_A$/L *(red)*, and 10 kU$_A$/L or greater *(green)*.
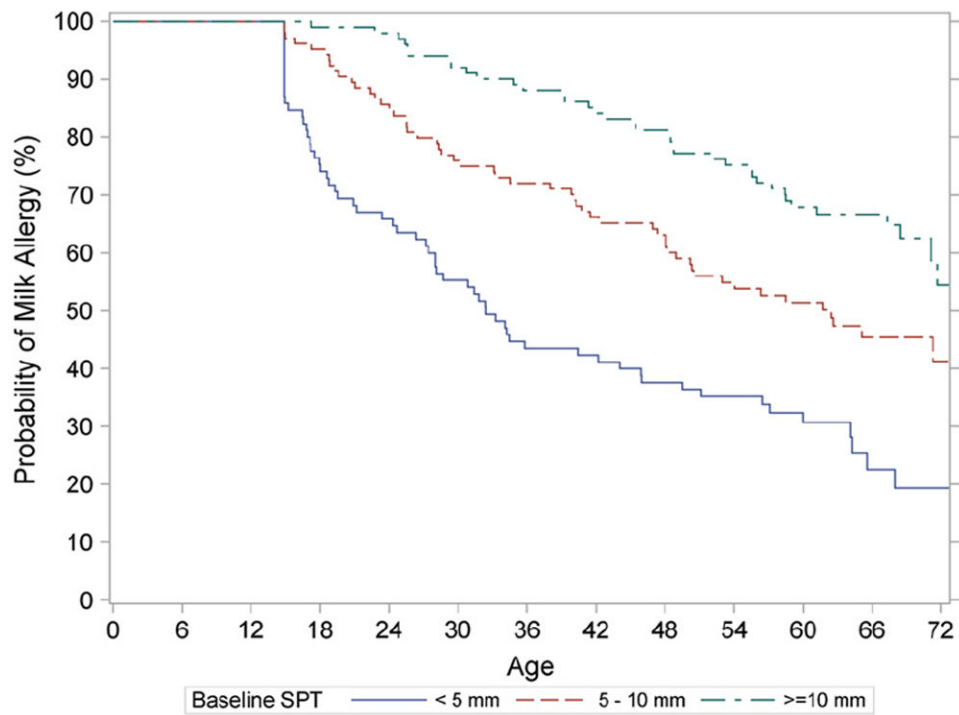
FIG 3.

Kaplan-Meier analysis representing the relationship of milk allergy resolution to baseline milk SPT wheal size. Individual curves represent wheal sizes of less than 5 mm *(blue)*, 5 to 10 mm *(red)*, and greater than 10 mm *(green)*.
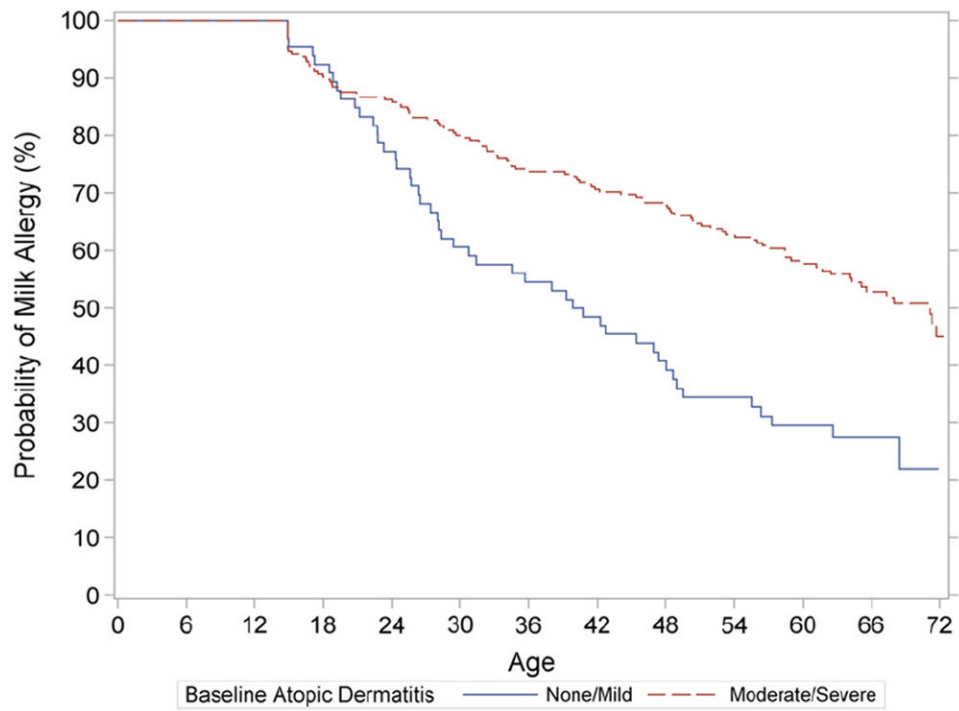
FIG 4.
Kaplan-Meier analysis representing the relationship of milk allergy resolution to baseline AD. Individual *curves* represent no/mild AD *(blue)* and moderate/severe AD *(red)*.
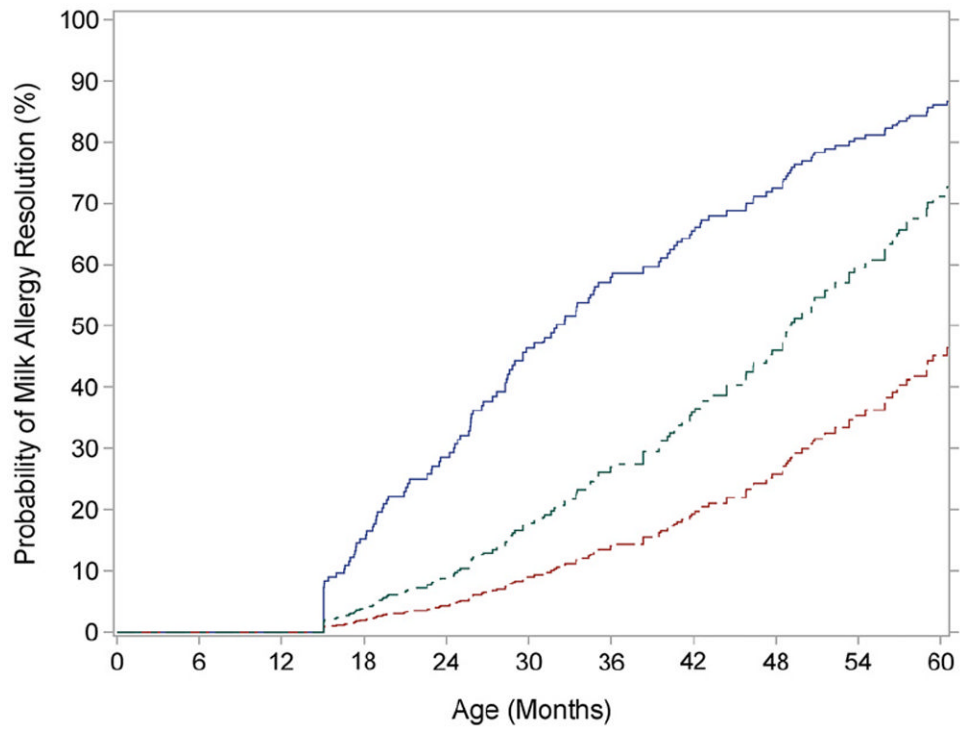
FIG 5.
This figure represents results of a composite index based on the baseline milk-specific IgE level, SPT wheal, and severity of AD, which can be used to estimate the likelihood of milk allergy resolution. For example, the *lower curve (red)* in this figure represents a patient with a milk-specific IgE level of 20 kU_A/L, an SPT mean wheal diameter of 7 mm, and moderate-to-severe AD, whereas the *middle curve (green)* represents a patient with the same IgE level and skin test score but no or mild AD. The *upper curve (blue)* represents another patient with a milk IgE level of 2 kU_A/L, an SPT wheal score of 4 mm, and no or mild AD.

TABLE I

Baseline characteristics

	All milk allergy, no.	Milk allergy resolved				P value*
		No		Yes		
		No.	Percent	No.	Percent	
Total subjects	293	139	47.4	154	52.6	
Baseline age (mo)						.93
3-5	37	16	43.2	21	56.8	
6-8	64	31	48.4	33	51.6	
9-12	114	56	49.1	58	50.9	
13-15	78	36	46.2	42	53.9	
Sex						.64
Female	101	46	45.5	55	54.5	
Male	192	93	48.4	99	51.6	
Race						.06
White	223	105	47.1	118	52.9	
Black/African American	41	17	41.5	24	58.5	
Asian	23	16	69.6	7	30.4	
Other	6	1	16.7	5	83.3	
Baseline milk IgE level (kU_A/L)†						<.001
<2	122	34	27.9	88	72.1	
2.0-10	85	39	45.9	46	54.1	
10	82	63	76.8	19	23.2	
Baseline milk SPT response (wheal, mm)‡						<.001
<5	86	24	27.9	62	72.1	
5-10	105	50	47.6	55	52.4	
>10	101	64	63.4	37	36.6	
Baseline AD severity						<.001
None	32	6	18.8	26	81.3	

	All milk allergy, no.	Milk allergy resolved				P value*
		No		Yes		
		No.	Percent	No.	Percent	
Mild	34	12	35.3	22	64.7	
Moderate	146	77	52.7	69	47.3	
Severe	81	44	54.3	37	45.7	
Breast-feeding at entry						.38
Never	41	18	43.9	23	56.1	
Yes, currently	106	56	52.8	50	47.2	
Yes, but no longer	146	65	44.5	81	55.5	
Other food allergy at baseline						.91
No	176	83	47.2	93	52.8	
Yes	117	56	47.9	61	52.1	
Baseline asthma and/or allergic rhinitis						.21
No	256	125	48.8	131	51.2	
Yes	37	14	37.8	23	62.2	

*Test for equivalence of resolution rates.

[†]Four subjects had missing milk-specific IgE values.

[‡]One subject had missing milk SPT values.

TABLE II

Resolution of milk allergy (Cox regression analysis with 1 variable in the model at a time)

Factor for resolution of milk allergy	Hazard ratio	95% Hazard ratio confidence limits	P value[*]
Baseline age (mo)			
3-5 vs 13-15	1.40	0.82-2.36	.378
6-8 vs 13-15	1.12	0.71-1.76	
9-12 vs 13-15	0.91	0.61-1.35	
Sex			
Female vs male	1.28	0.92-1.78	.141
Race			
White vs nonwhite	1.02	0.70-1.48	.909
Baseline milk-specific IgE level (kU_A/L)			
<2 vs 10	5.74	3.48-9.46	<.001
2-<10 vs 10	2.66	1.56-4.54	
Baseline AD			
Mild/none vs moderate/severe	2.09	1.48-2.94	<.001
Baseline milk SPT response (mm)			
<5 vs >10	3.65	2.42-5.51	<.001
5-10 vs >10	1.86	1.22-2.82	
Breast-feeding at entry			
Yes, but no longer vs never	0.94	0.59-1.49	.399
Yes, currently vs never	0.76	0.46-1.24	
Other food allergy			
Yes vs none	0.94	0.68-1.29	.687
Asthma or rhinitis			
Yes vs none	1.30	0.83-2.03	.246

[*] P values represent comparisons of all variables in that category.